FORM PTO-1390 (REV. 11-2000) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U.S. APPLICATION NO. (If known, see 37 CFR 1.5)
0471-0260P	09/830449

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP99/07887	October 18, 1999	October 30, 1998

TITLE OF INVENTION
A PROCESS FOR THE PREPARATION OF ALPHA-ARYLALKANOIC ACIDS

APPLICANT(S) FOR DO/EO/US
ALLEGRETTI, Marcello; CESTA, Maria Candida; MANTOVANINI, Marco; NICOLINI, Luca

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39 (1).
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau). WO 00/26176
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is transmitted herewith.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4)
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 20. below concern document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98-International Search Report (PCT/ISA/210) w/ 1 document
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821-1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. ☒ Other items or information:
    1.) PCT Substitute Claims Letter w/ International Preliminary Examination Report (PCT/IPEA/409) and claim 1
    2.) PCT Request (PCT/RO/101)
    3.) Zero (0) sheets of Formal Drawings

09830449 .050602

531 Rec'd PCT... 27 APR 2001

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
NEW 09/830449	PCT/EP99/07877	0471-0260P

21. ☒ The following fees are submitted:	CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5):		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO..... **$1,000.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO..... **$860.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO..... **$710.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)..... **$690.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)..... **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 860.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$ 130.00	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total Claims	12 - 20 =	0	X $18.00	$ 0	
Independent Claims	2 - 3 =	0	X $80.00	$ 0	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)		Yes	+ $270.00	$ 270.00	
TOTAL OF ABOVE CALCULATIONS =				$ 1260.00	
☒ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.				$ -630.00	
SUBTOTAL =				$ 630.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐20 ☐30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$ 0	
TOTAL NATIONAL FEE =				$ 630.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$ 0	
TOTAL FEES ENCLOSED =				$ 630.00	
				Amount to be: refunded	$
				charged	$

a. ☒ A check in the amount of $ **630.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account. No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-2448.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

Send all correspondence to:
Birch, Stewart, Kolasch & Birch, LLP or Customer No. 2292
P.O. Box 747
Falls Church, VA 22040-0747
(703)205-8000

Date: April 27, 2001

By _____ #32,868
for Raymond C. Stewart, #21,066

/cqc

PATENT
0471-0260P

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant:	ALLEGRETTI, Marcello et al.	Conf.:	
Int'l. Appl. No.:	PCT/EP99/07887		
Appl. No.:	New	Group:	
Filed:	April 27, 2001	Examiner:	
For:	A PROCESS FOR THE PREPARATION OF ALPHA-ARYLAKANOIC ACIDS		

PRELIMINARY AMENDMENT

BOX PATENT APPLICATION
Assistant Commissioner for Patents
Washington, DC 20231

April 27, 2001

Sir:

The following Preliminary Amendments and Remarks are respectfully submitted in connection with the above-identified application.

AMENDMENTS

IN THE SPECIFICATION:

Please amend the specification as follows:

Before line 1, insert --This application is the national phase under 35 U.S.C. § 371 of PCT International Application No. PCT/EP99/07887 which has an International filing date of October 18, 1999, which designated the United States of America and was published in English.

Docket No. 0471-0260P

REMARKS

The specification has been amended to provide a cross-reference to the previously filed International Application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By #32,868
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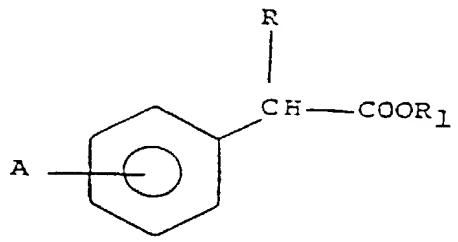
RCS/cqc
0471-0260P

(Rev. 02/12/01)

A PROCESS FOR THE PREPARATION OF ALPHA-ARYLALKANOIC ACIDS

The present invention relates to a process for the preparation of meta or para-substituted α-arylalkanoic acids.

More particularly, the invention relates to a process for the preparation of compounds of formula (I)

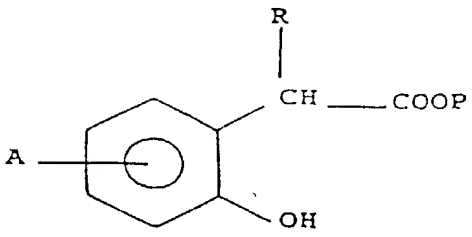


(I)

wherein:

R is hydrogen, C_1-C_6 alkyl; R_1 is hydrogen, straight or branched C_1-C_6 alkyl, phenyl, p-nitrophenyl, a cation of an alkali or alkaline-earth metal cation or of a pharmaceutically acceptable ammonium salt; A is C_1-C_4 alkyl, aryl, aryloxy, arylcarbonyl, 2-, 3- or 4-pyridocarbonyl, aryl optionally substituted with one or more alkyl, hydroxy, amino, cyano, nitro, alkoxy, haloalkyl, haloalkoxy; A is at the meta or para positions;

starting from compounds of formula (II)



(II)

(II)

in which P is straight or branched C_1-C_6 alkyl, phenyl, p-nitrophenyl.

Different strategies are at present used for removing the phenolic hydroxyl of arylalkanoic acids derivatives, based on the derivatization and subsequent elimination of the derivative by reduction, but in most cases such procedures suffer from drawbacks such as high-cost reagents or lack of selectivity.

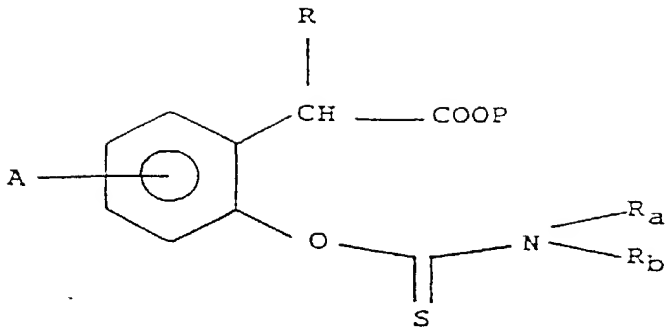
British Patent 2025397 (Chinoin), discloses the use of various derivatives of the phenolic hydroxyl, such as phenylaminocarbonyl, 1-phenyl-5-tetrazolyl, 2-benzoxazolyl, $-SO_2OMe$, and the reduction of the derivative with hydrogen on Pd/C catalyst.

WO 98/05632 application, in the Applicant's name, discloses the use of perfluoroalkanesulfonates, in particular trifluoromesylate, followed by reduction with formic acid and triethylamine in the presence of palladium acetate / triphenylphosphine complex.

It has now been found a process for the preparation of arylpropionic acids starting from the corresponding α-hydroxylated derivatives, using inexpensive reagents and keeping intact any reducible groups, such as esters or ketones, present on the side chains of the starting molecules.

According to the process of the invention, the compounds of formula (I) are prepared through the following steps:

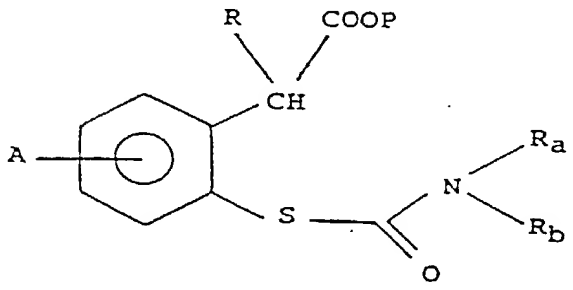
a) transformation of compounds of formula (II) into compounds of formula (III):



(III)

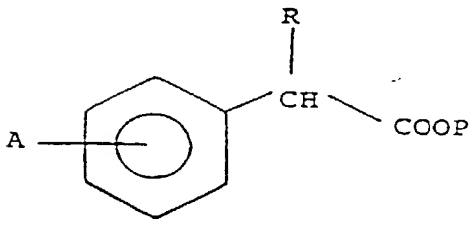
wherein R_a and R_b are C_1-C_6 alkyl, preferably methyl;

b) thermal rearrangement of compound (III) to give (IIIb)



(IIIb)

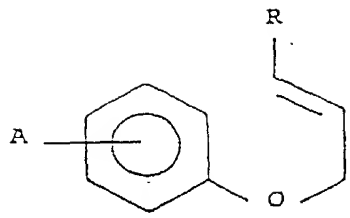
c) catalytic hydrogenation of (IIIb) to give (IIIc)



(IIIc)

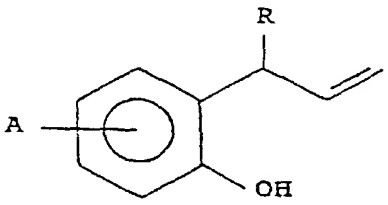
d) transformation of (IIIc) into (I).

The compounds of formula (II) can be prepared as described in WO 98/05623. Briefly, starting from arylolefins of formula (IV)



(IV)

wherein A and R have the same meanings as defined above, by Claisen rearrangement, compound (V) is obtained

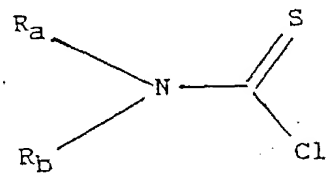


(V)

which can be subsequently subjected to oxidative cleavage, for example by ozonolysis or with potassium permanganate in phase transfer conditions, thus yielding the corresponding carboxylic acid product. The latter can be transformed into compound (II) by esterification with a suitable alcohol.

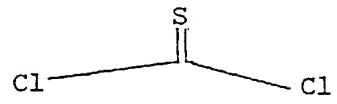
Step a) can be carried out in two ways.

In the first case, compound of formula (II) is reacted with

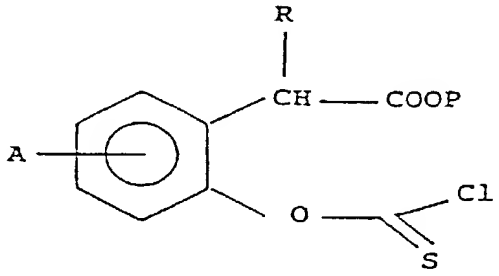


wherein R_a and R_b are as defined above, in the presence of an inorganic base such as an alkali or alkaline-earth carbonate, or an organic one, such as triethylamine or pyridine.

Alternatively, compound of formula (II) is reacted first with thiophosgene,



to obtain compound (IIIa)



(IIIa)

which is subsequently reacted with HNR_aR_b in which R_a and R_b are as defined above.

The conversion of the phenol in O-aryl-dialkylthiocarbamate by reaction with R_bR_aNCSCl, and the subsequent thermal rearrangement (step b) of the O-aryl dialkylthiocarbamate to give compound (IIIb), are described in Newman and Karnes, "The conversion of phenols", J. Org. Chemistry, Vol. 31, 1966, 3980-3982.

On the other hand, as for the preparation of the O-aryl-dialkylthiocarbamate by reacting the phenol with

thiophosgene and subsequently the resulting product with amine R_aR_bNH, the method reported in Can. J. Chem., 38, 2042-52 (1960) can be followed.

In step c), the catalytic hydrogenation of S-aryl-dialkylthiocarbamate (IIIb) to give (IIIc) can be carried out with Ni-Raney as catalyst.

Compound (IIIc) is easily converted to (I) through conventional procedures for the hydrolysis of the ester group and optional subsequent reesterification or salification of the carboxylic group.

The process of the invention proved to be particularly advantageous when group A in general formula (I) is an optionally substituted aroyl group, in that the carbonyl function is preserved during the reduction of the thiocarbamoyl derivative. For example, when A is benzoyl, no reduction of the ketone under the used experimental conditions is observed. Furthermore, as already mentioned, the process of the invention is based on the use of low cost reagents, provides good yields, requires no purifications of the intermediates and has a low environmental impact.

The following examples illustrate the invention in greater detail.

Example 1

Preparation of 2-(3'-benzoyl-2'-hydroxyphenyl)-propionic acid methyl ester (2)

A solution of 2-(3'-benzoyl-2'-acetoxyphenyl)propionic acid (1) (6.2 g) in methanol (35 ml) was added with concentrated H_2SO_4 (0.3 ml). The mixture was stirred at room temperature for 15 hours until disappearance (1) and of the reaction intermediates. The solvent was evaporated off under vacuum and the residue

was dissolved in ethyl acetate (30 ml) and washed with water. The organic layer was treated with a NaOH solution (100 ml), and the basic phase was acidified with 4N HCl and extracted with ethyl acetate (2 x 25 ml). The collected organic layers were washed with brine, dried over Na_2SO_4 and evaporated under vacuum. The crude product (4.3 g) was dissolved in isopropyl ether (5 ml) and the slightly yellow precipitate was filtered. n-Hexane (25 ml) was added to the residue and the mixture was stirred overnight. After filtration, 3.2 g of (2) were obtained (0.11 mol; 70% yield starting from 4) as a whitish solid (melting point 108-111°C).

TLC (CH_2Cl_2/MeOH 9:1 Rf = 0.45)

Elementary analysis calculated for $C_{17}H_{16}O_3$: C-71.81, H-5.67.

Found: C-71.16, H-5.63.

^{1}H-NMR ($CDCl_3$) d 8.4 (s, OH, 1H); 7.85-7.3 (m, 7H); 7.0 (d, 1H, J = 7 Hz); 3.95 (q, 1H, 8 Hz); 3.8 (s, 3H); 1.6 (d, 3H, J = 8 Hz).

Example 2

Preparation of 2-(3'-benzoyl-2'-O-dimethylthiocarbamoylphenyl)-propionic acid methyl ester (3)

A solution of (2) (3.2 g, 0.011 mol) in acetone (25 ml) was added with potassium carbonate (1.65 g, 0.012 mol) and the mixture was stirred at room temperature for 15 min. A solution of N,N-dimetilcarbamoyl chloride (1.51 g, 0.012 mol) in acetone (5 ml) was added drop by drop to the refluxed mixture for 2 hours. After cooling at room temperature, the precipitated inorganic salts were filtered off and the solvent was evaporated under vacuum. The residue was dissolved in ethyl acetate (25 ml) and washed with water (2 x 10 ml) and brine (2 x 10

ml). The organic phase was dried over Na_2SO_4 and evaporated under vacuum, to obtain 3.45 g of (3) as a dark oil sufficiently pure to be used in the subsequent step.

TLC (n-hexane/EtOAc 8:2) Rf = 0.25

Elementary analysis calculated for $C_{20}H_{22}NO_4S$: C-64.49, H-5.95, N-3.76, S-8.61.

Found: C-64.17, H-5.92, N-3.82, S-8.60.

^{1}H-NMR ($CDCl_3$) d 7.95-7.8 (m, 4H); 7.6-7.4 (m, 3H); 7.2 (d, 1H, J = 7 Hz); 3.9 (q, 1H, J = 8 Hz); 3.7 (s, 3H); 3.6 (s, 3H); 3.4 (s, 3H) 1.6 (d, 3H, J = 8 Hz).

Example 3

Preparation of 2-(3'-benzoyl-2'-S-dimethylthiocarbamoylphenyl)propionic acid methyl ester (4)

Compound (3) (3.45 g) was heated in a flask at T = 210°C (temperature of the outer oil bath) for 2 hours under stirring. After cooling at room temperature and evaporation under vacuum, 3.45 g of (4) were obtained (0.0054 mol) sufficiently pure to be used without further purifications.

TLC (n-hexane/ethyl acetate 8:2 Rf = 0.2).

Elementary analysis calculated for $C_{20}H_{22}NO_4S$: C-64.49, H-5.95, N-3.76, S-8.61.

Found: C-64.17, H-5.92, N-3.82, S-8.60.

^{1}H-NMR ($CDCl_3$) d 7.9-7.8 (m, 3H); 7.7-7.3 (m, 5H); 4.4 (q, 1H, J = 8 Hz); 3.65 (s, 3H); 3.2-2.9 (d broad, 6H); 1.6 (d, 3H, J = 8 Hz).

Example 4

Preparation of 2-(3'-benzoylphenyl)-propionic acid methyl ester (5)

Acetone (50 ml) was added to Ni-Raney (50% in water, 20 ml) and the water/acetone mixture was removed.

The treatment was repeated 3 times. Subsequently the catalyst was suspended in acetone (30 ml) and refluxed for 30 hours.

A solution of (4) (3.45 g) in acetone (4 ml) was added drop by drop and the mixture was refluxed overnight. After cooling at room temperature, the catalyst was filtered off and washed with acetone (10 ml). The filtrate was evaporated under vacuum, to obtain 2.4 g of (5) as a slightly brown oil.

TLC (n-hexane/ethyl acetate 9:1 Rf = 0.7)

Elementary analysis calculated for $C_{17}H_{16}O_3$: C-76.10, H-6.01.

Found: C-75.99, H-6.03.

^{1}H-NMR ($CDCl_3$) d 7.9-7.4 (m, 8H); 3.8 (q, 1H, J = 8 Hz); 3.65 (s, 3H); 1.6 (d, 3H, J = 8 Hz)

Example 5

Preparation of 2-(3'-benzoylphenyl)propionic acid (6)

The solution of (5) (2.4 g, 0.009 mol) in methyl alcohol (25 ml) was added with 1N NaOH (13.5 ml) and the mixture was left under stirring for 8 hours at room temperature. After evaporating the solvent, the residue was diluted with water and 5% monobasic sodium phosphate was added drop by drop to the mixture to adjust pH to 5. The aqueous layer was then extracted with methyl acetate (2 x 100 ml). The collected organic extracts were dried over Na_2SO_4 and evaporated under vacuum, then crystallized from a benzene/petroleum ether 6:20 mixture to obtain 2.05 g of (6) (0.0081 mol; yield 90%) as a white solid (melting point 92-92°C) following crystallization.

TLC ($CHCl_3/CH_3OH$ 95:5) Rf = 0.2

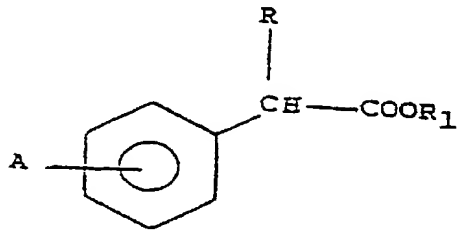
Elementary analysis calculated for $C_{16}H_{14}O_3$: C-75.57, H-5.55.

Found: C-75.19, H-5.53.

^{1}H-NMR ($CDCl_3$) d 7.91-7.75 (d, 3H), 7.74-7.51 (m, 2H), 7.50-7.35 (m, 4H), 3.85 (q, 1H, J = 10 Hz), 1.58 (d, 3H, J = 10 Hz).

CLAIMS

1. A process for the preparation of meta or para-substituted α-arylalkanoic acids of formula (I):



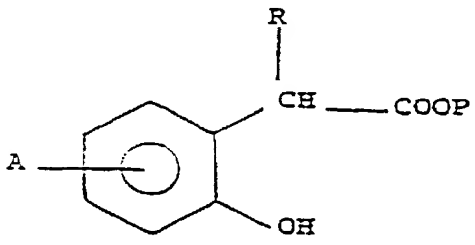
(I)

wherein:

R is hydrogen, C_1-C_6 alkyl; R_1 is hydrogen, straight or branched C_1-C_6 alkyl, phenyl, p-nitrophenyl, a cation of an alkali or alkaline-earth metal cation or of a pharmaceutically acceptable ammonium salt; A is C_1-C_4 alkyl, aryl, aryloxy, arylcarbonyl, 2-, 3- or 4-pyridocarbonyl, aryl optionally substituted with one or more alkyl, hydroxy, amino, cyano, nitro, alkoxy, haloalkyl, haloalkoxy; A is at the meta or para positions;

which process comprises the following steps:

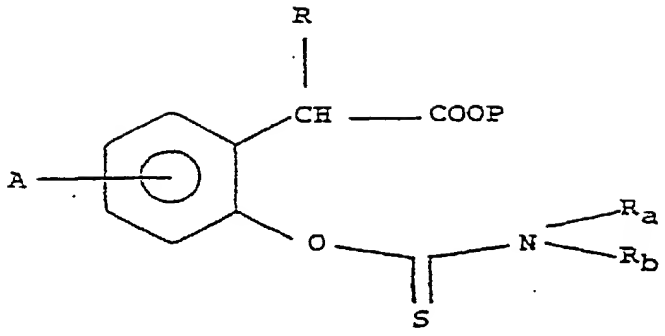
a) transformation of compounds of formula (II)



(II)

in which P is straight or branched C_1-C_6 alkyl, phenyl, p-nitrophenyl,

into compounds of formula (III)

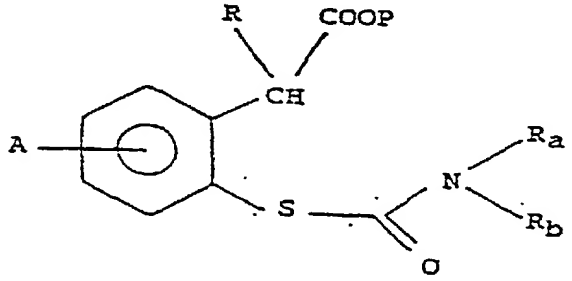


(III)

wherein

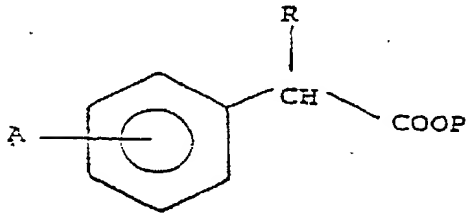
R_a and R_b are C_1-C_6 alkyl, ~~preferably methyl~~;

b) thermal rearrangement of compound (III) to give (IIIb)



(IIIb)

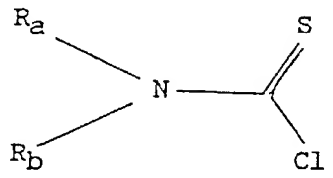
c) catalytic hydrogenation of (IIIb) to give (IIIc)



(IIIc)

d) transformation of (IIIc) into (I).

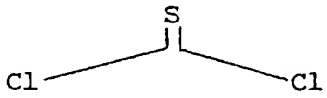
2. A process according to claim 1, in which the transformation of step a) is carried out by reaction of the compound (II) with



wherein R_a and R_b are as defined in claim 1, in the presence of an organic or inorganic base.

3. A process as claimed in claim 2, in which said organic base is selected from triethylamine and pyridine, and said inorganic base is selected from alkali or alkaline-earth carbonates.

4. A process as claimed in claim 1, in which the transformation of step a) is carried out by reaction of compound (II) with thiophosgene

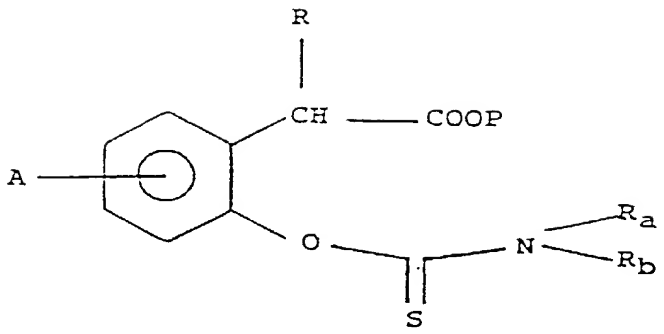


and subsequent reaction of the resulting product with HNR_aR_b, wherein R_a and R_b are as defined in claim 1.

5. A process as claimed in claim 1, in which the hydrogenation of step c) is carried out with Ni-Raney.

6. A process according to any one of the above claims, in which the group A of formula (I) is meta-benzoyl and R is methyl.

7. As a reaction intermediate, the compound

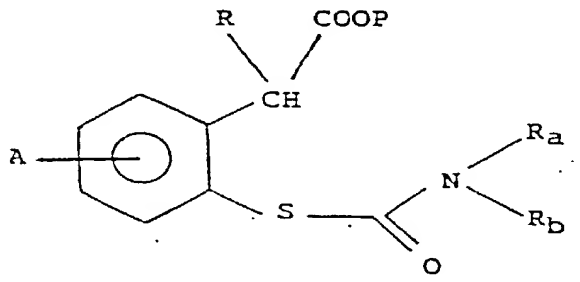


(III)

wherein:

R is hydrogen, C_1-C_6 alkyl; A is a C_1-C_4 alkyl, aryl, aryloxy, aryl optionally substituted with one or more alkyl, hydroxy, amino, cyano, nitro, alkoxy, haloalkyl, haloalkoxy, A is at the meta or para positions; P is straight or branched C_1-C_6 alkyl, phenyl, p-nitrophenyl; R_a and R_b are C_1-C_6 alkyl.

8. As a reaction intermediate, the compound



(IIIb)

wherein A, R, P, Ra and Rb are as defined in claim 7.

PCT

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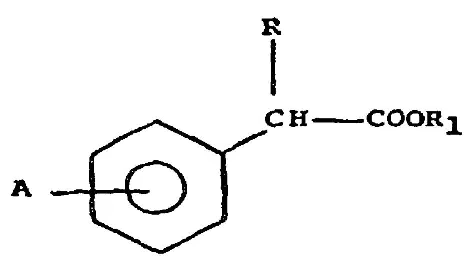
(54) Title: A PROCESS FOR THE PREPARATION OF ALPHA–ARYLALKANOIC ACIDS

(57) Abstract

A process for the preparation of meta or para–substituted α–arylalkanoic acids of formula (I) wherein R and R_1 are as defined in the disclosure.



(I)

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Insert Title: A PROCESS FOR THE PREPARATION OF ALPHA-ARYLALKANOIC ACIDS

Fill in Appropriate Information - For Use Without Specification Attached:

the specification of which is attached hereto. If not attached hereto,
the specification was filed on April 27, 2001 as
United States Application Number 09/830,449 ;
and amended on April 27, 2001 (if applicable) and/or
the specification was filed on October 18, 1999 as PCT
International Application Number PCT/EP99/7887 ; and was
amended under PCT Article 19 on (if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

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Prior Foreign Application(s)			Priority Claimed	
MI98A002332 (Number)	Italy (Country)	October 30, 1998 (Month/Day/Year Filed)	☒ Yes	☐ No
(Number)	(Country)	(Month/Day/Year Filed)	☐ Yes	☐ No
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